

REMARKS/ARGUMENTS

Independent claims 7, 14, 23, 39 have been revised to feature human subjects and RNA expression levels, which are supported at least by claims 75, 77, 84, 86, 93, 95, 102, 104, 109, and 112-115 as previously presented. Claims 75, 84, 93, and 102 have been canceled to correspond to the revisions in claims 7, 14, 23, 39 and 109.

Claims 7, 14, 23, and 39 have also been revised to include a description of the inherent meaning and intent of a “mean (average) ratio” as recited in the claims. Support for the revisions is found at least in Figures 3, 6, and 7 of the instant application. Claim 23 has also been revised to use alternative language in the preamble and to remove references to “therapeutic treatment.” Claim 39 has also been revised to correct a clerical oversight in the inclusion of “decreased” expression of IL17BR in the last subparagraph of the claim.

Claims 74, 76, 77, 83, 85, 86, 92, 94, 95, 101, 103, and 104 have been revised to correspond to the revisions to claims 7, 14, 23, and 39. Support is provided at least by claims 77, 86, 95, and 104 as previously presented.

Claims 78, 87, 96, and 105 have been revised to include the feature of “reverse transcription polymerase chain reaction”. Support is provided at least at page 15, lines 12-15; page 19, lines 3-8; and page 40, lines 19-25 of the instant application.

Claims 79, 88, 97, and 106 have been revised to include the feature of a “formalin fixed paraffin embedded (FFPE)” sample. Support is provided at least at page 52, lines 20-27, and by Figures 6 and 7 of the instant application.

Claim 117 has revised to correct a clerical oversight in the intended language of the claim.

Claims 118-121 have been canceled without prejudice for re-presentation in a continuing application.

No new matter has been introduced, and entry of the above amendments is respectfully requested.

Summary of Telephonic Interview

Applicants thank Examiner Qian for the courtesy of a telephonic interview with the undersigned as well as co-inventors Mark Erlander and Xiao-Jun Ma on July 22, 2008. The discussion centered on proposed revisions to claims 7, 14, 23, and 39 essentially as presented above. The discussion also included consideration of documents by Jansen et al. and Jerevall et al. Applicants thank Examiner Qian for indicating that progress has been made in advancing the application toward allowance and for indicating that a favorable response was likely when the revised claims are presented formally and with a discussion of relevant documents.

Drawings

The Action mailed June 26, 2008 includes a Requirement for revised drawings. Applicants understand the requirement to include the need to revise the vertical axes in Figures 3, 6, and 7. Applicants are prepared to submit substitute sheets containing revised versions of Figures 3, 5, and 7 which indicate "log2 of IL17BR expression", "log2 of HOXB13 expression" and "log2 of CACNA1D expression" as appropriate in the vertical axes in Figures 3 and 6; and which indicate "log2 of HOXB13/IL17BR" in the vertical axes in Figure 7. But Applicants respectfully ask for confirmation of these proposed changes as sufficient to address the Requirement.

Additionally, Applicants request clarification of the Requirement with respect to the labeling of the horizontal axes. Applicants are uncertain as to the exact changes that are required.

Applicants also request clarification of the statement regarding "all of the figures ... on the previous version of the sheet." Is this a Requirement for inclusion of the sheet containing "FIG. 7 (con't.)" where no changes were necessary?

Applicants stand ready to comply with the Requirement for revised drawings upon clarification of the above.

Alleged claim rejections under 35 U.S.C. § 112, first paragraph

Claims 7, 14, 23, 39, and 74-121 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to be supported by an enabling disclosure. Applicants have carefully reviewed the statement of the rejection and respectfully traverse because no *prima facie* case of non-enablement is present. Reconsideration and withdrawal of the instant rejection is respectfully requested.

As an initial matter, Applicants point out that this rejection has been obviated with respect to claims 118-121, which have been canceled without prejudice as explained above.

With respect to the remaining claims, Applicants respectfully, but strongly, traverse the instant rejection. The instant rejection alleges that the claims are too broad, that there is inadequate guidance and working examples, unpredictability in the art, and a need for a large amount of experimentation. But Applicants point out that the ultimate determination is whether undue experimentation is needed to make and use the claimed invention. It is well settled that the presence of enablement does not mean the lack of experimentation. To the contrary, routine and/or repetitive experimentation is the opposite of undue experimentation and is clearly permitted under U.S. patent law. Applicants respectfully submit that no more than routine and/or repetitive experimentation is needed to make and use the claimed invention.

For example, a review of the pending claims shows that the components of the claimed subject matter are all known to the skilled person based upon knowledge in the art and the instant application as filed. With respect to claims 7, 14 and 23, the skilled person is knowledgeable regarding ER+ breast cancer in human subjects, various means to obtain a sample of breast cancer from such a subject, assaying the sample for HoxB13 and IL17BR RNA expression levels, calculating a ratio of expression levels, and comparing the ratio to a mean. With respect to claim 39, the skilled person is knowledgeable regarding ER+ breast cancer in human subjects, various means to obtain a sample of breast cancer from such a subject, assaying the sample for HoxB13 and IL17BR RNA expression levels, and comparing the levels to a mean for each. Given such knowledge and familiarity, there are simply no undue levels of unpredictability or experimentation needed to make and use the claimed invention.

For these reasons alone, the instant rejection may be properly withdrawn.

Turning to the specific contentions asserted in the statement of the instant rejection, Applicants address them in the order presented.

With respect to the statements on page 5 of the Action concerning claim 14, Applicants point out that contrary to the asserted contentions, claim 14 expressly recites the alternatives of “a cancer-free outcome” and “an outcome comprising cancer recurrence” within the body of the claim. Therefore, the scope of the claim is not so broad as to support an allegation of non-enablement.

With respect to the statements regarding HoxB13 and IL17BR sequences on pages 6 and 7, Applicants point out that as explained in the instant application and known to the skilled person, knowledge in the relevant field includes the existence of a genus of HoxB13 sequences and a genus of IL17BR sequences. The instant application includes express examples of specific exemplary sequences as representative species of sequences that may be used in the practice of the claimed invention. The instant application also includes representative examples of using specific sequences and their detection via a microarray based system.

As discussed during the telephonic interview of July 22, 2008, the instant application’s stated use of additional species of HoxB13 and IL17BR sequences for use in the practice of the invention has been demonstrated by other groups. For example, the Ma et al. (Cancer Cell 5:607-616, 2004) and Jansen et al. (J. Clin. Oncol. 25(6):662-668, 2007) documents describe the detection of specific sequences via a quantitative PCR based system, which is distinct from the microarray based system exemplified in the instant application. And while Ma et al. (2004) report the detection of one HOXB13 sequence and one IL17BR sequence, Jansen et al. report detecting expression of HOXB13 by different commercially available “Assay-on-Demand kits” for Hs00197189_ml (HOXB13) and Hs00914532_ml (IL17BR 3’ region) as well as Hs00218889_ml (IL17BR 5’ region used by Reid et al., J. Natl. Cancer Inst. 97:927-930, 2005). See page 664, left column, second full paragraph. In that same passage, Jansen et al. state that the two IL17BR sets “amplify two published variants described in the Entrez Gene database.” And in the paragraph bridging pages 667-668, Jansen et al. state as follows:

For their analysis of *IL17BR* expression levels, Reid et al.⁴ used a primer set in the 5' end region of *IL17BR*, whereas Ma et al.² applied a primer set in the 3' end region. Because of the difference in primer design, we have evaluated both primer sets. The 3' end primer set (ps3) of *IL17BR* revealed $6 \times$ higher expression levels compared with levels determined with a 5' end primer set (ps5). Despite this six-fold difference, levels of both correlated significantly. As a consequence, corresponding *HOXB13*-to-*IL17BR* ratios showed equivalent performances.

So in combination, Ma et al. (2004) and Jensen et al. used two *HOXB13* sequences and two *IL17BR* sequences. One of these was the set of *IL17BR* primers used by Reid et al. as cited by Jensen et al.

There is also work reported by Ma et al. (J. Clin. Oncol. 24(28):4611-4619, 2006), where an additional *HOXB13* sequence and an additional *IL17BR* sequence were detected (see page 4612, paragraph bridging left and right columns, reporting the use of different primers and probes from that of Ma et al. (2004)).

In light of these demonstrations consistent with the content of the instant application, Applicants respectfully submit that there is no need to speculate as to “expression of the other sequences of the human HoxB13 and *IL17BR* family [being] correlated with responsiveness to tamoxifen treatment in ER+ breast cancer” as contended on page 7, last sentence, of the Action. Therefore, the content of the application is wholly consistent with the presence of an enabling disclosure.

With respect to the statements regarding a “mean ratio”, “appropriate treatment”, and “decrease of *IL17BR*” on pages 8 and 9, Applicants point out that the claims as revised obviate the issues raised by the statements. With respect to the “decrease of *IL17BR*” in claim 39, Applicants point out that Example 4 of the instant application describe statistically significant results from detecting *IL17BR* expression, which are shown in Figures 3 and 6. This is consistent with Ma et al. (2006, J. Clin. Oncol. as cited above and provided herewith), who

summarize data regarding the statistically significant association between IL17BR expression with disease-free survival as follows in the paragraph bridging pages 4613-4614:

Using the entire cohort, univariate Cox regression analysis indicated that gene expression levels of *ER*, *PR*, *HOXB13*, *IL17BR*, and *CHDH*, treated as continuous explanatory variables, were all significantly associated with RFS (Fig 2). Specifically, higher expression of *HOXB13* and lower expression of *IL17BR* or *CHDH*, and a higher *HOXB13:IL17BR* index were all associated with a higher risk of relapse, in a manner similar to that in our original study.¹¹

So in addition to the disclosure of the instant application, Ma et al. (2006) provides confirmatory evidence of a statistically significant association between decreased IL17BR expression and a higher risk of cancer recurrence.

And while the above discussed data may be contrasted against the results in Figure 1C, left panel, of Jerevall et al., Applicants point out that a careful review of that panel shows that it is indicated as having a P value of 0.061 (see lower left corner of panel), which is greater than the reliable level of P=0.05. Therefore, Applicants respectfully submit that this single panel fails to introduce any reasonable doubt regarding the association demonstrated in the instant application and observed by Ma et al. (2006).

Based on the above discussion, Applicants submit that no support for a contention of non-enablement is present from the statements on pages 8 and 9.

With respect to the statements regarding the state of the prior art on pages 9-12, Applicants respectfully point out that the limitations reported by van't Veer et al., Wu, and Lucentini are overcome by the advances provided by the instant application and encompassed by the pending claims. Therefore, and regardless of the accuracy of contending that the art is "underdeveloped" or that additional studies with larger sample sizes are necessary, Applicants point out that the claimed subject matter reflects an advance that overcomes the statements by

van't Veer et al. and Wu as well as the post-filing statements of Lucentini. The presence of an advance in the instant application is supported by the documents of Jansen et al. and Jerevall et al., as discussed during the telephonic interview, as well as those of Goetz et al. (previously cited) and Ma et al. (2006; as provided herewith).

Given the presence of significant, consistent, and confirmatory reports by at least Jansen et al., Jerevall et al., Goetz et al., and Ma et al. (2006), Applicants respectfully submit that no *prima facie* ("more likely than not") case of non-enablement can be established based upon the generic reports of van't Veer et al., Wu, and Lucentini.

And with respect to statements based upon the report of Chen et al. on page 11, Applicants respectfully point out that the claims have been revised to feature RNA expression levels and so the Chen et al. document is not relevant.

In light of the foregoing, Applicants respectfully submit that no issue of non-enablement is present, and this rejection may be properly withdrawn.

Alleged claim rejections under 35 U.S.C. § 112, second paragraph

Claims 77 and 117 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Applicants respectfully point out that both claims have been revised such that no issue of indefiniteness remains. Reconsideration and withdrawal of this rejection is respectfully requested.

Alleged claim objections

Claims 74 and 102 were objected to as being of improper dependent form. Applicants point out that claim 74 has been revised to feature determining the expression levels of "mRNAs" while claim 7 features expression levels of RNA. Additionally, claim 102 has been canceled.

Reconsideration and withdrawal of this rejection is respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 425-681-1833.

Respectfully submitted,

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